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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/467,901	12/21/1999	JOOST VAN NEERVEN	02405.0190	2936

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EXAMINER	
DO, PENSEE T	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/467,901	Applicant(s) NEERVEN, JOOST VAN	
	Examiner Pensee T. Do	Art Unit 1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 July 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112, 1st paragraph.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-6 and 8-23*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 8/12/04
13. ☐ Other: _____.

SCOD

Advisory Action

Amendment Entry & Claim Status

The after final amendment filed on July 6, 2005 has been acknowledged and entered.

Claims 1-6, 8-23 are pending.

Withdrawn Rejection

Rejection under 112, 1st paragraph is withdrawn herein.

Maintained Rejection(s)

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-14, 16, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) further in view of Johnson et al. (US 6,034,066) and Frank et al. (US 6,060,326).

Johansen et al. teach a method of detecting an antibody in a sample using a labeling compound and comprising the steps of mixing the ligand antigen, antibody or hapten bound to biotin with the sample; an antibody is directed against the antibody to be detected bound to a paramagnetic particles; and a chemiluminescent acridinium

compound bound to avidin or streptavidin to form a solid phase complex; separating the solid phase from the liquid phase; and analyzing the separated solid phase for the presence of chemiluminescent complex. There are several embodiments. In one embodiment, the method comprises the following steps: mixing the ligand antigen, antibody or hapten bound to biotin or a functional derivative thereof with the samole and the antibody directed against the antibody to be detected bound to paramagnetic particles to form a first solid phase complex; adding a chemiluminescent acridinium compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex; magnetically separating the solid phase from the liquid phase; initiating the chemiluminescent reaction, and analyzing the separated solid phase for the presence of the chemiluminescent complex. Johansen et al. also teaches the method for the quantification of specific antibodies, such as immunoglobulins, wherein a truly parallel reference immunoassay using an identical protocol as a reference. The method comprises measuring the concentration and/or the relative contents of a specific antibody in a liquid sample, wherein the measured light emission of a separated solid phase comprising a captured specific antibody coupled to a chemiluminescent label is compared with the measured light emission obtained in a parallel reference immunoassay wherein the total contents of the class of antibodies in the sample to which said specific antibody belongs is measured. The method comprising the steps of mixing a ligand antigen, hapten towards which the specific antibody to be measured is directly bound to biotin or a functional derivative thereof; an antibody directed against the constant portion of the antibody to be measured bound to paramagnetic particles and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof with

the sample to form a first solid phase from the liquid phase; magnetically separating the first solid phase from the liquid phase; initiating a chemiluminescent reaction and measuring the light emission of the separated first solid phase; mixing a ligand antibody directed against the class of antibodies to be measured bound to biotin or a functional derivative thereof; an antibody directed against the constant portion of the class of antibodies to be measured bound to paramagnetic particles ; and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof wherein the term total shall mean the entire amount of the designated class of immunoglobulins (e.g. IgA, IgE, etc.) With the sample to form a second solid phase complex, magnetically separate the second solid phase form the liquid phase; initiating the light emission of the separated first solid phase with that of the separated second solid phase. The specific antibody to be measured in the sample is preferably a specific immunoglobulin selected from the group consisting of IgA, IgD, IgE, IgG, IgM and subclasses thereof. (See col. 3, line 30-col. 5, line 45).

However, Johansen et al. fails to teach using an IgE receptor to bind IgE antibody/ligand complexes and a method of quantification of IgE wherein the IgE to be detected is quantified using both CD23 alone to obtain a first measurement and using FcORII alone to obtain a second measurement. Johansen fails to teach a "method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody or a hapten in a liquid sample suspected to contain the IgE antibody by simulating in vivo interactions between IgE antibody, the IgE antibody's ligand and the IgE antibody's receptor".

Johnson et al. teach multiple important roles of CD23 in the regulation of immune responses, particularly the regulation of IgE responses. Among these roles, CD23 acts as a cellular receptor for IgE and is found in various cell types including B cells. (See col. 1, line 31-col. 2, line 64).

Frank et al. teach detecting IgE antibodies using a human Fc epsilon receptor FcOR. (See col. 1, line 45-col. 2, line 10).

It would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson et al. and Frank et al. to measure IgE according to the method of Johansen et al. since both of these receptors, CD23 and FcOR, are specific to IgE antibody and because FcOR and CD23 can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. (See Frank et al. Col. 1, lines 19-34). Regarding claim 16, wherein the number of ligand molecules is between 100% and 200 % of the number of IgE molecules to be detected, it would have been obvious to one of ordinary skills in the art to use enough ligand molecules to optimize binding of all the IgE molecules to be detected. In order to detect 100% of the IgE present in the sample, at least 100% of ligand molecules must be present to bind all the IgE present in the sample. Regarding claim 23, in view of the 112, 2nd paragraph, the preamble "simulating in vivo interactions" is not given any patentable weight.

Claims 6, 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) in view of Frank et al. (US 6,060,326) further in view of Arnold, Jr. et al. (US 6,004,745).

Johansen et al. and Frank et al. have been discussed above.

However, Johansen and Frank fail to teach adding label after a first separation step and a second separation to separate the non-complexed labels.

Arnold, Jr. discusses in the background section that a typical sandwich assay involve incubating an immobilized antibody (IgE receptor) with a test medium (sample). Antigens, if in the medium, will bind to the antibody. After incubation, unbound antigen is removed in a separation step. After a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes sandwiched between the immobilized antibody and the labeled antibody. After a second separation step, the amount of labeled antibody can be determined as a measure of the antigen in the medium. (see col. 1, lines 55-66).

It would have been obvious to one of ordinary skill in the art to add the label molecule after a first separation step and then separating the non-complexed labels as discussed in Arnold, Jr. using the reagents in the method of Johansen modified by Frank because such second separation steps, although time consuming, increases the sensitivity of the assay results. Furthermore, since the non-complexed immobilized antibody and the non-complexed labels are separated one at a time, cross-reactivity between the label and the immobilized antibody/reagent is eliminated.

Response to Arguments

Applicant's arguments filed on July 6, 2005 have been fully considered but they are not persuasive.

Regarding the 103 rejection by Johansen in view of Johnson and Frank 2., Applicant basically submit the same arguments, as in the previous response, that Johansen and Frank 2 do not use the same set of reagents, Johansen uses antibodies to

detect the presence of IgE, not IgE receptors. In contrast, Frank 2 uses at least an IgE receptor and may or may not use other reagents like antibodies to bind different portions of an IgE molecule. Johnson merely provides a discussion as to the functions of CD23 in the immune system without any reference to using this receptor in the method of detecting or quantifying IgE. Thus, Applicant argues that the Office improperly uses hindsight in suggesting that it would have been obvious to use CD23 or FccR in the method of Johansen or that it would have been obvious to optimize detection or quantification by binding all the IgE molecules in the samples. Applicant's final argument pertains to a lack of reasonable expectation of success. Applicant argues that Johansen and Frank 2 use different steps and different reagents in their methods and that the Office has not provided evidence to suggest that there was an expectation that one could successfully extrapolate the use of reagent (FccR1 receptor) utilized under a particular set of conditions (Frank 2) and expect it to work as a replacement of another reagent (anti-IgE antibody) under a different set of conditions (Johansen). And Johnson does not mention the use of an IgE receptor in the method of detecting an IgE antibody. Applicant also mentions that the Fc receptor taught by Frank 2 is a canine receptor, not a human Fc receptor. Applicants also submit that the two references that may use similar components do not necessarily use them in the same way and therefore do imply that such components can be used interchangeably.

Since Applicants' arguments in this response are somewhat similar to those in the previous response, the Office's response in the previous office action still remains.

Applicants submit that the first new citation in Frank 2 in the previous office action refers to canine receptors, not human receptors.

In response, Applicants' invention fails to exclude a canine receptor. Applicants have not mentioned or recited any requirement that the IgE receptor must a human receptor. Thus, the canine IgE receptor in Frank 2 still applies.

With regards to the second new citation, Applicants argue that Frank 2 does not teach in what capacity such particulates would be used in the assay. Two references may use similar components do not necessarily use them in the same way.

In response, Applicants' attention is directed to Frank 2, col. 10, lines 15-35, where Frank 2 teaches that:

> In one embodiment a complex can be formed and detected in solution. In another embodiment, ***a complex can be formed in which one or more members of the complex are immobilized on (e.g., coated onto) a substrate***. Immobilization techniques are known to those skilled in the art. Suitable substrate materials include, but are not limited to, plastic, glass, gel, celluloid, paper, PVDF (poly-vinylidene-fluoride), nylon, nitrocellulose, and ***particulate materials such as latex, polystyrene, nylon, nitrocellulose, agarose and magnetic resin***. Suitable shapes for substrate material include, but are not limited to, a well (e.g., microtiter dish well), a plate, a dipstick, a bead, a lateral flow apparatus, a membrane, a filter, a tube, a dish, a celluloid-type matrix, a magnetic particle, and other particulates. A particularly preferred substrate comprises an ELISA plate, a dipstick, a radioimmunoassay plate, agarose beads, plastic beads, latex beads, immunoblot membranes and immunoblot papers. In one embodiment, a substrate, ***such as a particulate***, can include a detectable marker.

And lines 50-60, where Frank further teaches that:

> A preferred immunoabsorbent assay method includes a step of either: (a) ***binding a canine Fc.sub..epsilon. R molecule to a substrate prior to contacting a canine Fc.sub..epsilon. R molecule with a putative IgE-containing composition to form a canine Fc.sub..epsilon. R molecule-coated substrate***; or (b) binding a putative canine IgE-containing composition to a substrate prior to contacting a canine Fc.sub..epsilon. R molecule with a putative IgE-containing composition to form a putative IgE-containing composition-coated substrate. Preferably, the substrate is a non-coated substrate, an antigen-coated substrate or an anti-IgE antibody-coated substrate.

Thus, Frank 2 uses the particulate-based assay in the same way as that of Johansen because Frank teaches binding the Receptor to a substrate prior to contacting with a putative IgE-containing composition. The substrate is used in Frank for the purpose of capturing the target IgE containing composition being detected. Johansen also uses the same substrate/magnetic particles for the same purpose, which is to capture the IgE being detected

A reasonable expectation of success has been explained in the previous office action pages 9-10 and is once again established herein:

The motivation to combine the references has been clearly established in the previous office action. Johansen teaches a method for the quantification of specific antibodies such as immunoglobulins (IgE, IgA, ..). The sample containing the specific antibody is mixed with a ligand antigen (free dissolved ligand of the present invention); an antibody directed against a constant portion of the antibody to be measured bound to a paramagnetic particles and a chemiluminescent acridinium compound as a label; magnetically separating the bound from the unbound; and detect. Johnson uses a CD23 (a reagent directed against a constant portion of the antibody to be measured (IgE antibody)), which is specific for IgE antibody being detected. Frank teaches detecting IgE antibodies using a human Fc epsilon receptor (Fc0R). Such Fc eplison receptor is specific to the IgE of the IgE antibody being detected. Thus, it would have been obvious to one of ordinary skill in the art to use CD23 or Fc0R as an IgE receptor to measure IgE antibody because these receptors can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. Regarding claim 16, it is obvious for an ordinary skill in the art to optimize the result by binding all the IgE molecules to be

detected. Regarding Applicants' analysis of the two references about "solid supports vs. suspension of particles", it is well known that solid supports can include particles and Frank teaches that his reagents can be detected using particulate-based immunoassay (particulates such as magnetic particles, polystyrene, latex beads). Furthermore, whether a solid support or a particles is used, the antibody/ligand must bind to the solid support or a particle and a step of capturing must be performed. Thus, there is no difference between the reagents of the two methods.

Once again, Applicant fails to point out any factors that would prevent the combined references from having a reasonable expectation of success.

Since the deficiencies, as submitted by the Applicants, in Frank and Johansen have been explained and cured. It is unnecessary to discuss the reference by Johnson.

Regarding the 103 rejection by Johansen in view of Frank 2 and Arnold, Applicants argue that Arnold does not cure the deficiency of motivation as discussed above. Arnold's method does not use an IgE receptor or mention the use of an IgE receptor. Rather, Arnold uses two antibodies, one immobilized to a surface and the other labeled. With respect to claims 17-19, the Office has not explained why one skilled artisan would replace only the immobilized antibody with an IgE receptor to arrive at the present invention instead of replacing both antibodies, which as alleged by the Office, may provide more specificity and sensitivity to the method.

Regarding the Arnold references, Applicant argues that Arnold's method does not use an IgE receptor or mention the use of an IgE receptor. Rather, Arnold uses two antibodies, one immobilized to a surface and the other labeled. The office has not explained why one skilled in the art would replace only the immobilized antibody with an

IgE receptor to arrive at the invention instead of replacing both antibodies, may provide more specific and sensitive to the method. There is no teaching that such a single replacement would offer any particular advantage over a double replacement. Applicant also argues that the Office has not explained why one would be motivated to use two separation steps in the method of Johansen and Frank 2. Arnold also does not teach an assay that mimics in vivo interactions.

Arnold is relied upon for the second separation step. While a separation step is necessary and well known in the art in an assay after adding a reagent such as a carrier or a label to a mixture of samples containing the target compound, it is necessary to provide a reference that teaches such a separation step. While Johansen and Frank 2 both teaches adding a label to the complex, they fail to teach a separation step to separate the unbound labels and the bound labels. However, one skilled in the art would know to carry out a separation step in order to have meaning results. Without a separation step after adding a label, no meaningful detection can be done because not all the labels bind to the target. Furthermore, when using a label to detect a target compound, one would label the target compound directly. Thus, in the method of Johansen and Frank 2, the IgE is being detected, and thus the label must have some means to bind to the IgE. Such means is either an antibody against IgE such as one taught by Johansen or an IgE receptor taught by Frank 2. Either the IgE antibody or the IgE receptor would serve the same purpose that is to attach the label to IgE specifically. Thus, one of ordinary skills in the art would be able to figure out which reagent to use and would have a reasonable expectation of success to arrive at the present invention. Discussion of a single replacement of IgE receptor over a double replacement is unnecessary because Arnold is relied upon for the

general teaching of using separation steps to separate bounds from unbound. Separation steps are known in the art for eliminating non-specific bindings, cross-reactivity and increasing sensitivity of the assay results. One of ordinary skills in the art would have been motivated to use two separation steps because the first separation is to eliminate non-bound carrier (immobilized antibodies) and the second separation step is to eliminate non-bound labels. In any sandwich assay wherein the reagents (immobilized antibodies and then labels) are added one at a time, separation steps must be performed after each addition of each reagent (immobilized antibodies and labels). These separation steps are well known in the art.

Regarding the limitation of "simulating an in vivo interaction" in claim 23, Applicant now added in step (b) that "wherein the complexes that comprise the IgE antibody and the ligand are formed prior to contact with an IgE receptor to simulate in vivo interactions between the IgE antibody, the ligand, and the IgE receptor". Since the combination of Johansen, Frank 2, Johnson and Arnold teaches that the IgE antibody and the ligand are formed prior to contact with an IgE receptor, they meet the requirement for simulating in vivo interactions between IgE antibody, the ligand and the IgE receptor because the newly added limitation merely requires that in order to simulate in vivo interactions, the IgE antibody and the ligand must form prior to contact with an IgE receptor.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
August 22, 2005

LONG V. LE
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09/05/05